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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/217,324	03/24/1994	WILLIAM R.A. OSBORNE	163363	9058

7590 03/25/2002

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	36

DATE MAILED: 03/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/217,324	Applicant(s) OSBORNE ET AL.	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is an original application filed March 24, 1994.

Applicants' amendment filed January 8, 2002, paper number 35 has been received and entered. Claims 6-22 have been amended. Claims 1-22 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Applicants argue that the instant specification provides adequate support and guidance to make the instantly claimed device. See Applicants amendment page 7. Applicants arguments have been fully considered and found persuasive.

The basis of the previous rejection was directed to the intended use of the instantly claimed device as applied to the methods of introducing and expressing a gene of interest in a subject. Upon review of the specification, Examiner would agree that the instant specification

provides adequate guidance for the creation of an *ex vivo* graft device as instantly claimed. Further, though the art supports aspects of unpredictability for implantation and the intended use for the *in vivo* delivery of a gene of interest, the art of record fully supports that the instantly claimed device can be manufactured. In addition, the instant invention finds use *in vitro* for assaying different methods for the transduction and/or transfection of vascular smooth muscle cells and a means to monitor transgene expression.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

First, it is noted that amendments to the claims have obviated the basis of the rejections set forth in the previous office action.

Claims 1, 5-10 are unclear and indefinite in the recitation of 'autologous smooth muscle cell' because the term "autologous" can only be defined relative to the individual into or for which it will be used. In the instant case, the claims are drawn to a generic product and as such, the term "autologous" provides no context to define this term. For example, the same device with smooth muscle cells from one individual may be both autologous if used in the same

individual or heterologous if used in another individual or animal. The term "autologous" seems to be drawn to the intended use of the product, however the claim is drawn to a generic product and thus, the intended use does not define the metes and bounds of the claims because the use is subject to change. Claims 2-4 are included in the basis of the rejection because they depend on the autologous cells of claim 1, however fail to clarify the basis of the rejection. Amending the claim to be a product by process may provide a context to properly define the metes and bounds of the term "autologous". It is noted, that claims 21 and 22 recite the term 'autologous serum', however, since this is a method, autologous would be defined by the artisan as serum derived from the same individual from which the cells are derived, though the resulting product would be generic to any smooth muscle cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4, 6, 11, 12 and 15 rejected under 35 U.S.C. 102(a) as being anticipated by Osborne *et al.* is withdrawn.

Applicants point out that the authors on the cited reference are exactly the same as the instant inventors and argue that this reference, being a 102(a) does not constitute prior art by another. See Applicants' amendment page 6, last two paragraphs.

Applicants' arguments are persuasive, and therefore, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noishiki *et al.* (IDS reference, ASAIO Journal, 1992), Noishiki *et al.* (IDS reference, US Patent 5,171,261) and Zalewski *et al.* (WO 93/15609, 1993).

Claims 1 is drawn to a device comprising an elongated tube and vascular smooth muscle cells transduced with a transgene, wherein the cells are immobilized on the graft surface, claims 2-4 and 9 encompass a porous device made of PTFE, dacron or nylon with immobilized cells for

use as a vascular graft. Claim 10 encompasses a graft wherein endothelial cells are further added to the graft. Claims 11, 20-22 encompass a method for making a vascular graft wherein the cells are seeded onto the grafting material *ex vivo*. Claims 5-8 and 12-19 are drawn to the expression of specific gene products. The specification provides general guidance for the isolation and transduction of vascular smooth muscle cells and their deposition onto grafting material, and provides a working example of a graft comprising transduced cells.

At the time of the claimed invention, both Noishiki *et al.* (ASAIO Journal, 1992), Noishiki *et al.* (US Patent 5,171,261) teach a vascular prosthesis. Specifically, each describe the use of porous elongated tubes for the seeding and deposition of vascular smooth cells and endothelial cells for the use in generating a vascular graft. Each provide evidence that cells can be seeded and fixed to the grafting material. Noishiki *et al.* (ASAIO Journal, 1992) use only a Dacron material (page M158, second column), however Noishiki *et al.* (US Patent 5,171,261) more completely describe the breadth of materials and combination of vascular cells which can be deposited (column 2; line 60-column 5; line 46). In addition, Noishiki *et al.* (ASAIO Journal, 1992) provides a detailed summary of use and outcome of various grafts for vascular transplantation and description of the limitations of their use. In particular, while the devices are suitable for small diameter arterial grafts, the accumulation of thrombi resulting in occluded grafts presents an existing obstacle. Noishiki *et al.* (ASAIO Journal, 1992) use heparin as an anti-clotting factor, however this material is quickly released from the graft offering short term affects (page M160, summarized in figure 3). In summary, both Noishiki *et al.* provide the

necessary guidance to produce a device for implantation wherein vascular cells are deposited onto a porous tubular membrane. Noishiki *et al.* (ASAIO Journal, 1992) provide evidence that use of the device results in a graft lined with vascular cells, but is still limited because of secondary vascular problems such as clotting. Noishiki *et al.* provide evidence that the use of heparin provided preliminary short term success however, neither Noishiki *et al.* teach to provide a vascular smooth muscle cell transduced with a gene of interest. At the time of the claimed invention Zalewski *et al.* teach the use of vascular muscle cells for the expression of interferon in the treatment of vascular disorders. Specifically, Zalewski *et al.* teach that vascular smooth muscle cells transformed with polynucleotides to express interferon result in the inhibition of intra-vascular blockage (summarized in abstract). Further, Zalewski *et al.* provide a summary of the art teaching that other transgene products can also be produced such as anticoagulants, EPO, urokinase, insulin, and clotting factors such as Factor IX (listed on page 3). In view of the detailed guidance given by both Hoishiki *et al.* references for the generation vascular grafts, and the teaching that problems for use of these grafts still exist and the rapid loss of proteins administered to ameliorate said problems, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to substitute the methods of Zalewski *et al.* for a more long term treatment solution to vascular disorders associated with the graft. Further, though the specific teachings of Zalewski *et al.* provide the detailed guidance for the use of polynucleotides expressing interferon, given the general review of what was known in the art and the guidance for the transduction of vascular smooth muscle cells taught by Zalewski *et al.* it

would have been *prima facie* obvious to substitute other transgenes, in particular proteins which are known to be anticoagulants, as a substitute to heparin for the prevention of thrombi seen in the grafts of Hoishiki *et al.* (page M161, summarized in figures 4 and 5). In view of the quick loss of heparin from the graft taught by Hoishiki *et al.* one of skill in the art would have been motivated to find more long term solutions for the generation of proteins which would be therapeutic to vascular disorders. The teachings of Zalewski *et al.* for the expression of proteins in smooth vascular muscle cells provides one such long term solution.

With respect to Applicants' arguments regarding the teaching of Zalewski *et al.* presented in the declaration of Dr. Osborne, paper number 29, it is noted that the instant rejection does not rely on the specific methodology of *in vivo* transduction or cellular explanation of transduced cells as taught in Zalewski *et al.* In the instant rejection, Zalewski *et al.* is relied upon to provide the teachings for a more long term solution in the treatment of vascular disorders, not the specific methodology to deliver a polynucleotide *in vivo*. There is nothing in the teachings of Zalewski *et al.* which would lead the artisan away from using any of the transgenes specifically taught in the reference. Further, as noted in Applicants' arguments, the art recognized (as supported in the art by Nabel *et al.* see paper number 29, page 4 section 12) that the simple methodology for the introduction transformed cells had recognized limitations. In view of this specific teaching of Nabel *et al.* to the known limitations recognized in the art, one of skill in the art would have been motivated to provide a more efficient means for the delivery of transduced vascular cells and would have identified Hoishiki *et al.* as an alternative means for

the delivery of such cells. Though the instant rejection is presented initially with the teachings of Hoishiki *et al.*, there is adequate motivation in the art to also view the teachings and limitations provided by Zalewski *et al.* and identify the teachings of Hoishiki *et al.* as an alternative means for the delivery of vascular smooth muscle cells to those disclosed in Zalewski *et al.*

The ability to transduce a cell in culture to produce a protein of interest is routine, however it is noted that the level of skill in the art is high for the generation grafts for the intended use of transplantation. The art recognized the preliminary success and limitations of artificially constructed grafts, and given the detailed guidance of both Hoishiki *et al.* and Zalewski *et al.* there would have been a reasonable expectation of success to generate a vascular graft which comprises transduced vascular muscle cells which encode the proteins set forth in the instant claims.

Thus, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Patsy Zimmerman whose telephone number is (703)308-8338.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

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